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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,309	02/21/2002	Michael Brandt	20859	3846

151 7590 03/30/2005

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER	
CHANDRA, GYAN	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,309	BRANDT ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-15* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/04/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8, 12-15, drawn to a conjugate consisting of a NK4 molecule and a polyethylene glycol group and a pharmaceutical composition comprising a conjugate consisting of a NK4 molecule and a polyethylene glycol group and –CO group of PEG forms amide bond with one of the amino group of N-terminal fragment of the NK4, classified in class 530, subclass 402.

II. Claims 9-11, drawn to a method of treatment comprising administration of pharmaceutical composition comprising a conjugate of NK4 molecule and mono-PEGylated with polyethylene glycol groups, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons: Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the conjugate molecule of Invention I could be used to generate antibodies.

Searching the Inventions of Groups I and II together would impose a serious search burden. In the instant case, the search of the conjugate molecule and the method of using the conjugate molecule are not coextensive. The inventions of Groups I and II also have a separate status in the art as shown by their different classifications.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different methods of use, restriction for examination purposes as indicated is proper.

This application contains claims directed to the following patentably distinct species of the claimed invention:

A. A polyethylene glycol group has the formula of:

i) $-CO-(CH_2)_x-(OCH_2CH_2)_mOR$

ii) $-CO-CH[(NHCO(OCH_2CH_2)_pOR\ ]\ [(C\ H_2)_yNHCO(OCH_2CH_2)\ _nOR]$

Claims 1 is generic to a plurality of disclosed patentably distinct species comprising the polyethylene glycol groups with distinct formulas. Each of the polyethylene glycol group formula is considered to constitute a patentably distinct species because they include distinct structural and functional complexities, and require separate searches, for example NPL. Search of more than a single species would constitute an undue burden on the Office.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, 1 is an example of a generic claim.

B. A polyethylene glycol group is selected from:

iii) monomethoxy polyethylene glycol groups

iv) a linear PEG chain group

v) a branched PEG chain group

Claims 1 is generic to a plurality of disclosed patentably distinct species comprising the polyethylene glycol groups. Each of the polyethylene glycol group is considered to constitute a patentably distinct species because they include distinct structural complexities, and require separate searches, for example NPL and structure

searches. Search of more than a single species would constitute an undue burden on the Office.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 9 are examples of a generic claim.

C. The polyethylene attachment to the NK4 at:

vi) a lysine reside

vii) a N-terminal residue

Claims 1 is generic to a plurality of disclosed patentably distinct species comprising the polyethylene attachment to the NK4 residues. Each of the polyethylene attachment to the NK4 residues is considered to constitute a patentably distinct species because they include distinct structural and technical complexities, and require separate searches, for example NPL and structure searches. Search of more than a single species would constitute an undue burden on the Office.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, 1,6 are generic claims.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims

readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

If Applicant selects Group I, one species from the polyethylene glycol formula group, one species from the polyethylene glycol group, and one species from the polyethylene glycol attachment group must be chosen to be considered fully responsive. If Applicant selects Group II, one species from the polyethylene glycol attachment group must also be chosen to be considered fully responsive.

During a telephone conversation with Frank Hoffman on 12/22/2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-8, and 12-15. Affirmation of this election must be made by applicant in replying to this Office action. Claims 9-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants elected the following species as per requirement:

(i) $-CO-(CH_2)_x-(OCH_2CH_2)_mOR$ from Group A, Iii) monomethoxy polyethylene glycol groups from group B and (iii) a N-terminal residue from group C

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of Application, Amendments, And/Or Claims

Claims 1-15 are pending. Claims 3, 7, and 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention.

Claims 1-2, 4-6, 8, and 12-15 will be examined on the merit to the extent that they read on the elected species (i) $-CO-(CH_2)_x-(OCH_2CH_2)_mOR$, (ii) monomethoxy polyethylene glycol groups and (iii) a N-terminal residue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-6, 8, and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Namiki et al (EP 0816381 A1, published on 07/01/1998) in view of Date et al (Oncogene, 17:3045-3054, 1998) and Gaertner et al (Bioconjugate 7: 38-42, 1996).

The claimed invention is drawn to a conjugate consisting of a NK4 molecule and a polyethylene glycol group having a molecular weight of about 20-40 kDa wherein polyethylene glycol group has: (i) the formula–CO-$(CH_2)_x$-$(OCH_2CH_2)_m$OR, (ii) is

monomethoxy polyethylene glycol and (iii) forms amide group with the amino groups of N-terminal NK4 fragment.

Namiki et al teach how to modify hepatocyte growth factor (HGF) by attaching a polyethylene glycol (PEG), and a pharmaceutical composition comprising the PEG modified HGF (page 12, line 37-40). They teach that the modification of HGF by attaching monoethoxy linear and branched PEG(s) at the N-terminus amino acids to improve the clearance and in vivo pharmacokinetics of HGF (page 2, line 49-57). Namiki et al teaches HGF but not explicitly NK4 which is a molecule comprising four-kringle domains of HGF. Namiki et al also fail to teach the attachment of PEG having the molecular weight of 20 to 40 kDa.

Date et al disclose that within HGF is a four-kringle-containing (NK4) growth factor which affects the growth and invasiveness of carcinoma cells. They teach that the NK4 is a 59 kDa protein which comprises four-kringle domains and functions as an antagonist in mitogenic, morphogenic and tumor inhibitory activities of HGF (page 3046, 2nd paragraph of the left column).

Gaertner et al teach attaching PEG at amino terminus of proteins and suggest that a PEG in size from 5 to 40 kDa should be attached to a protein for an improved bioavailability (page 44, first sentence of the 2nd paragraph of conclusion). Further, they suggest that a higher molecular weight PEG could be attached at a single attachment point using oxime bond (page 44, 2nd paragraph of conclusion). Polyethylene glycol comprises repeat units of (CH2) and (OCH2CH2), and the molecular weight of a PEG would depend on number of repeats it contains.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to attach PEG molecules in the range of molecular weight 5-40 kDa (as suggested by Gaertner) to the N-terminus amino acid of NK4 in order to increase clearance, improve in vivo pharmacokinetics as taught by Namiki with a HGF protein, and to prepare a pharmaceutical composition comprising the PEGylated protein. The person of ordinary skill in the art would have been motivated to attach NK4 as opposed to HGF with a reasonable level of success because Date et al show that NK4 molecule has antagonistic activities of HGF.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Namiki et al in view of Date et al and Gaertner et al as applied to claims 1-2, 4-6, 8, and 12-13 above, and further in view of and further in view of Veronese et.al. (US Patent 6,528,485 B1).

The claimed invention is drawn to a pharmaceutical composition comprising conjugates of NK4 monopegylated with PEG that have molecular weight of 20-40 kDa where conjugate comprises at least 90% or 92% pegylated NK4 and unpegylated NK4 molecules in the composition.

The teachings of Namiki et.al. in combination of Date et al and Gaertner et al are summarized as set forth supra. Namiki et.al. in combination of Date et al and Gaertner et al do not teach a pharmaceutical comprising at least 90% or 92% of pegylated NK4 and unpegylated NK4 molecules. Veronese et.al. teach making PEGylated proteins and

purifying them to greater than 92% purity. Veronese et al teach that with high purity a PEGylated protein would result in a better bioavailability and pharmacokinetics in vivo.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra
AU 1646
15 March 2005

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600